HIMA

HEALTH INDUSTRY MANUFACTURERS ASSOCIATION

June 15, 2000

Ms. Leanne Cusumano
Regulatory Counsel, Regulatory Policy Staff
Office of the Center Director
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont Office Complex 2, HFD-7
1451 Rockville Pike
Rockville, MD 20852

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Re: Final Rule on Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition Published January 26, 2000
(Docket No. 90N-0056)

Dear Ms. Cusumano:

On behalf of HIMA's Large Volume Parenteral Systems Task Force, I have enclosed a summary of the meeting between the Task Force and FDA representatives on June 1, 2000, concerning the final rule on aluminum referenced above. This summary records the agreements that were reached to move forward on implementation of the final rule. We look forward to receiving a copy of the FDA meeting minutes, to help ensure that the agency and the Task Force have a consistent view of the June 1 meeting discussion.

At the June 1 meeting, the agency requested follow-up from the Task Force concerning specific LVP and PBP (pharmacy bulk pack) products for which modification by reformulation or repackaging does not appear to be an option to ensure compliance with the final rule's aluminum limit of 25μg/L. The companies with LVP and PBP products that are members of the Task Force (Abbott Laboratories, Baxter Healthcare Corporation, and B. Braun Medical) will be submitting this information as individual companies directly to FDA as soon as possible.

FDA representatives made it clear in the June 1, 2000 meeting that PBPs used as LVPs should be considered to be LVPs under the January 26, 2000 final rule. We understand that this means these products must meet the 25 μg/L aluminum limit. We would like further agency clarification on the labeling requirements for these products. It is our proposal that PBPs used as LVPs follow the labeling requirements for LVPs specified in the final rule. This would include modification of the "Precautions" section of the package insert to state that the drug product contains no more than 25 μg/L of aluminum. Since these products are considered to be LVPs, the immediate container labels would not need to be modified. We are requesting Agency clarification on this issue.

90N-0056

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Thank you very much for arranging the June 1 meeting. We thought it was a very positive and productive discussion. As suggested, I will plan to contact Jane Axelrad during the week of June 26, 2000, to follow-up on how the agency plans to move forward on several of the issues we discussed.

Please feel free to contact me with any questions about the enclosed meeting summary. My direct dial phone number is (202) 434-7225 and my email address is mtandy@himanet.com.

Sincerely,

Marlene K. Tandy

Marlene K. Tandy, M.D., J.D.
Director, Technology and Regulatory Affairs
and Associate General Counsel

cc: Dockets Management Branch

HEALTH INDUSTRY MANUFACTURERS ASSOCIATION

Meeting Summary – HIMA Large Volume Parenteral Systems Task Force and FDA Re: Aluminum Labeling - June 1, 2000

Meeting Participants:

FDA – Center for Drug Evaluation and Research - Jane Axelrad, J.D. (CDER); Yuan-Yuan Chiu, Ph.D. (ONDR); Eric Coleman, M.D. (DMEDP); Leanne Cusumano, J.D. (RPS); Chuck Hoiberg, M.D., (ONDC); David Lewis, Ph.D., (ONDC II); Dave Read, J.D. (RPS); Duu-Gong Wu, Ph.D. (OWDC).

Industry – Jose Joseph, Ph.D. (Abbott Laboratories, R&D); Russell Madsen (Parenteral Drug Association); Karen Malik (Baxter Healthcare Corporation); Marcia Marconi (Baxter Healthcare Corporation); Frank Pokrop (Abbott Laboratories); Lisa Skeens, Ph.D. (Baxter Healthcare Corporation); John Spoden (B. Braun Medical, Inc.); Marlene Tandy, M.D., J.D. (HIMA); Martin Van Trieste (Abbott Laboratories, QA).

Purpose of Meeting:

HIMA's LVP Systems Task Force requested this meeting to discuss seven industry issues related to the FDA's final rule on aluminum labeling as outlined in HIMA's letter to FDA (Jane Axelrad) dated April 17, 2000.

Industry Issues and Proposals:

The seven industry issues and proposed solutions are summarized in the attached presentation from the June 1, 2000 meeting.

Meeting Discussion and Resolution:

Issue 1 – Inadequate Time for Final Rule Implementation

The HIMA Task Force elaborated on points from the April 17 letter to explain why the one year implementation time in the final rule is not sufficient. These details supporting industry's request for additional time include: (1) raw material supplier issues (e.g. raw material suppliers have been contacted and have little interest or incentive to assist manufacturers in lowering aluminum levels or testing for aluminum as these products are only a small percentage of their business), (2) manufacturers must develop validated analytical methods to qualify the material from vendors, including the purchase of capital equipment and training of personnel, as well as incorporation of testing into routine QC testing at facilities, (3) the analytical method must be converted from R&D mode into a robust method for batch release on a regular basis, and (4) appropriate labeling changes

(and CBE submission) can only occur after the analytical methods are validated and available to provide the aluminum concentration information on a regular basis.

The FDA representatives listened to these details and stated that the agency is not in a position to provide a decision on this issue at this time. The FDA representatives anticipate discussing this issue further among themselves to determine an appropriate response. The FDA representatives raised the possibility of addressing this issue in a guidance document.

The participants agreed that industry would continue to move forward to implement the provisions of the final rule in an expeditious manner. The participants anticipated that industry will submit to FDA some supplements by 1/26/01.

Issue 2 – Insufficient Space on Immediate Container Labels of SVPs

The HIMA Task Force circulated an art work example of an Abbott Laboratories Vitamin K 1mL ampule label to illustrate just how small the type would need to be in order to meet the terms of the final rule for this small size label.

The FDA representatives suggested the possibility that manufacturers can address this issue by using the existing regulatory process of applying to the agency for a labeling exemption for specific products that have small labels. The FDA representatives agreed to consider whether this point could be referenced in a guidance document, possibly as a "Frequently Asked Questions" type of document.

Issue 3 – LVP Products that Will Not Meet The Required Aluminum Limit

It was acknowledged that Dr. Lewis had been in contact with individual companies to inquire which products fall into this category.

The HIMA Task Force noted that there is a serious public health concern if premix products that are not able to meet the required aluminum limit are removed from the market at the one-year effective date of the final rule (1/26/01) and thereafter pharmacists nationwide begin to add separate ingredients on their own to TPN solutions. The FDA representatives agreed that they do not want to create any product shortages.

Some of these products are slightly over the 25μg/L aluminum limit, but contain not more than 50μg/L aluminum. If these premix solutions are taken off the market, pharmacists likely will compound these admixtures using the SVP products on the market. Such compounding increases the risk of a product misadventure, as discussed in a 1994 FDA safety alert.

The FDA representatives asked whether it would be possible for all products to meet the requirements of the final rule through reformulation or by converting from glass to plastic. The HIMA Task Force stated that some products contain aluminum levels above

25μg/L, up to 50μg/L, and for some of the more concentrated products, it may not be feasible to reduce the aluminum level below 25μg/L.

The FDA representatives requested that the manufacturers provide the agency with a list of the products that the companies believe will not be able to meet the 25μg/L aluminum limit for LVPs, even given a three-year implementation period for these specific products. This would make it more possible for the agency to address specific product situations, possibly in the format of a guidance document.

There was a discussion about PBPs (pharmacy bulk packs) that are used as LVPs. Dr. Chiu referred to the final rule, pages 4104 (3rd col.) and 4106 (1st col.), to provide the following interpretation: if the PBP is used as an LVP, then it has the same 25μg/L aluminum limit as LVPs.

Issue 4 – Release Data for Aluminum Required for Submission

The FDA representatives agreed with the industry proposal, indicating the proposal was consistent with the final rule.

Issue 5 – Labeling Clarification for SVPs and PBPs

The FDA representatives agreed with the industry proposal, indicating the proposal was consistent with the intent of the final rule.

Issue 6 – Agreement of Uniform Approach to Aluminum Testing on Stability

The FDA representatives agreed with the industry proposal, indicating that the proposal was the minimal acceptable frequency. The FDA representatives noted that manufacturers may choose to use additional testing points, but that the testing points in the industry proposal (time zero, annually thereafter, and at expiry) are sufficient.

Issue 7 – Clarification of the Scope of the Final Rule

The FDA representatives agreed that the final rule on aluminum labeling applies only to LVP and SVP drug products used for TPN, and not to medical devices (e.g. flush syringes.) The FDA representatives agreed that the final rule on aluminum labeling does not apply to multiple electrolyte solutions used for hydration or replacement. The FDA representatives also agreed that the final rule on aluminum labeling does not apply to the list of products presented in the industry overhead: 0.45% and 0.9% Sodium Chloride, 5% Dextrose, Lactated Ringers, Multiple Electrolyte Solutions defined by USP (e.g. Dextrose/Sodium Chloride/Potassium Chloride), and Heparin, because these products are not used in TPN.

Follow-up Steps:

Ms. Cusumano stated that the HIMA Task Force's April 17 letter, the presentation from today's meeting, and the FDA minutes of this meeting, would be submitted to the FDA docket for the aluminum final rule (FDA Docket No. 90N-0056). Ms. Cusumano and Dr. Tandy agreed to exchange written minutes of the meeting.

The HIMA Task Force agreed to provide the FDA with the list of products referenced above in the discussion of Issue 3. The FDA representatives agreed that the HIMA Task Force could contact the agency in three weeks to inquire about how the agency plans to move forward to address Issues 1, 2, and 3.

* * * *

Submitted by:

Marlene K. Tandy

Marlene K. Tandy, M.D., J.D.
Director, Technology and Regulatory Affairs
and Associate General Counsel

Date: 6/14/2000

Final Rule on Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition

HIMA LVP Task Force Meeting
with FDA Representatives
May 18, 2000

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Objective/Agenda

OBJECTIVE:

- Determine Agency acceptability of industry proposals regarding implementation of the Aluminum Final Rule

AGENDA:

- Inadequate Time for Final Rule Implementation
- Insufficient Space on Immediate Container Labels of SVPs
- LVP Products that Will Not Meet the Required Aluminum Limit
- Release Data for Aluminum Required for Submission
- Labeling Clarification for SVPs and PBPs
- Agreement on Uniform Approach to Aluminum Testing on Stability
- Clarification of the Scope of the Final Rule
- Discussion

Issue 1: Inadequate Time for Final Rule Implementation

- Final Rule requires implementation of all aspects of final rule within one year of publication (1/26/00)
- Numerous technical, manufacturing, supplier and regulatory issues present unusual hurdles for industry to comply with this implementation date
- Number of products and applications affected is significant
  - More than 500 products and 85 NDAs impacted for task force firms

Industry Proposal: Inadequate Time for Final Rule Implementation

- Industry will implement the required aluminum warning statement in the "Warnings" section of the PI for all LVPs, SVPs and PBPs within 1 year of final rule publication
- Industry will implement all other provisions of the final rule within 2 years of final rule publication
  - Modify LVP package inserts to state that the drug product contains no more than 25 µg/L of aluminum. This will be contained in the "Precautions" section.
  - Modify SVP and PBP immediate container labels to contain the statement "Contains no more than _ µg/L of aluminum"
  - Submit "CBE" Supplements to affected NDAs/ANDAs incorporating labeling changes, methods validation information, and batch data

Issue 2: Insufficient Space on Immediate Container Labels of SVPs

- It is not physically possible to add a legible aluminum statement on SVPs with restricted space on immediate containers
  - Many of these products already have labeling exemptions, and we request a variance to the final rule for this circumstance as well

Industry Proposal:

- The relevant aluminum statement may be located on the multi-container package for SVP products with restricted label space on the immediate container
  - For example, on the folded box which contains several ampoules

Issue 3: LVP Products that Will Not Meet the Required Aluminum Limit

- Final Rule requires LVP drug products to contain no more than 25 µg aluminum.
- Aluminum levels can be lowered by screening raw materials and shortening expirations. A limited number of products will still be above 25 µg aluminum limit.
- Reformulating and changing immediate container materials will likely bring these products into acceptable limits, but this will take at least 2-3 years.
  - Development activities include studies, sterilization and stability studies. Prior FDA approval will also be required.
- If these products need to be withdrawn on 1/26/01, there may be an adverse impact on public health and safety because there may be no alternative products available

Industry Proposal: LVP Products that Will Not Meet the Required Aluminum Limit

- Industry requests a variance to the final rule for these particular products
- Specified LVP products not able to meet 25 µg/L aluminum limit without reformulation/repackaging will meet the elements of the final rule required for SVPs and PBPs for an interim period not to exceed 3 years after publication of the final rule
  - This will include modification of the LVP immediate container labels to contain the statement "Contains no more than _ µg/L of aluminum"
- This variation will allow these specific drug products to remain on the market until they can be modified, and in the interim will notify clinicians of the aluminum content so they can make informed decisions for their patients

Issue 4: Release Data for Aluminum Required for Submission

- Final rule requires release data for several batches be included in the CBE supplements
- Industry requests that historical batch release data or stability data be sufficient for submission purposes as this would meet the intent of the requirement for batch release data
  - This is particularly important for product codes that are extremely low in production volume and therefore only manufactured infrequently

Industry Proposal:

- Historical batch release or stability data for several batches should be sufficient for CBE purposes
- A commitment could be included in the CBE submission to submit batch release data for aluminum for several batches as it becomes available

Issue 5: Labeling Clarification for SVPs and PBPs

- Final Rule requires the max level of aluminum present at expiry be stated on the immediate container of all SVPs and PBPs
- For SVPs and PBPs that will have a max level of aluminum below 25 µg/L industry would like the option to label the products: *"Contains no more than 25 µg/L of aluminum"*
  - This would significantly simplify process of determining max levels at expiry for these products that have very low levels
  - Likely to prevent unmeaningful labeling revisions in future years
  - Max level of 25 µg/L of aluminum was determined to be suitable for LVPs and therefore should be acceptable for SVPs as well. Also, it may not be clinically relevant whether a product is labeled with a maximum of 15 µg/L or 25 µg/L of aluminum

Industry Proposal: Labeling Clarification for SVPs and PBPs

- Industry should have the option to label the immediate container of SVPs and PBPs with the statement *"Contains no more than 25 µg/L of aluminum"* if the maximum level of aluminum at expiry for the drug product will be less than 25 µg/L
- A specific number derived from the three options outlined in the final rule should not be required

Issue 6: Agreement of Uniform Approach to Aluminum Testing on Stability

- Products impacted by the final rule will require aluminum testing on stability.
- Industry requests that FDA agree to common stability testing intervals for aluminum testing

Industry Proposal:

- Industry will conduct testing for aluminum at time zero, annually thereafter, and at expiry

Issue 7: Clarification of the Scope of the Final Rule

- Industry would like to confirm that the final rule applies only to LVPs, SVPs and PBPs used in TPN therapy
  - For example it does not apply to following LVPs:
    - 0.45 and 0.9% Sodium Chloride
    - 5% Dextrose
    - Lactated Ringers
    - Dextrose/Sodium Chloride/Potassium Chloride
    - Heparin
- We also want to confirm that it applies only to drug products, and not to solutions regulated as medical devices (i.e. flush syringes)